REMARKS

Applicants would like to thank Examiner Sheikh for taking the time to discuss the Final Office Action with their attorney on November 20, 2003. During the telephone interview, the Examiner pointed out that the claims were not allowed because the phrases "a magnesium component comprising" and "an interactive component comprising" did not exclude a magnesium component that included an interactive calcium component, nor an interactive calcium component that included a magnesium component.

The applicants would also like to thank Examiner Sheikh and Primary Examiner Kishore for their courtesy in discussing the Advisory Action mailed on January 20, 2004 with the applicants' attorney on February 9, 2004. The Primary Examiner pointed out that compositions consisting essentially of magnesium or calcium are not suitable for ingestion, but magnesium compounds and calcium compounds can be ingested.

Amendments to the Claims

Claims 1, 2, 5-8, 10, 11, 13-15, 17 and 18 have been amended. Claims 4 and 16 have been cancelled.

Applicants have amended claims 1, 14 and 15 to change "comprising" to "consisting essentially of" in order to exclude the possibility that either the magnesium component or the calcium component can include both a magnesium component and an calcium component. Support for the amendments is found at page 12, lines 3-5 and page 23, lines 16-17 of the specification which read:

> The magnesium component can be essentially magnesium or a magnesium compound such as magnesium citrate, magnesium carbonate, magnesium hydroxide, magnesium gluconate, magnesium oxide, magnesium sulfate, magnesium phosphate or magnesium aspartate.

and

> In a preferred embodiment, the first component is essentially calcium or a calcium compound and the second component is essentially magnesium or a magnesium compound.

The applicants have amended the claims to limit the magnesium component to one or more magnesium compounds or combinations thereof and the calcium component to one or more calcium compounds or combinations thereof. Support for these amendments is found in the specification at page 8, lines 4-6 and 9-11, which state:

> The magnesium component can be a magnesium compound such as magnesium citrate, magnesium gluconate, magnesium oxide, magnesium carbonate, magnesium hydroxide, magnesium sulfate, magnesium phosphate, magnesium aspartate or combinations thereof.

and

> When the interactive agent component is calcium, it can be present as calcium carbonate, calcium citrate, calcium propionate, calcium gluconate, calcium sulfate, calcium ascorbate or combinations thereof.

Claims 2 and 10 have been amended to state that the "release controlling agent is an enteric coating." Support for these amendments is found in the specification at page 7, lines 12-13.

> The controlled-release component can be an enteric coating having a pH dissolution point of from about 5 to about 8 and preferably from about 6.5 to about 7.2.

Claim Rejections - 35 USC § 103

Claims 1-12 and 15-17 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,042,849 to Richardson et al. ("Richardson" or "the `849 patent"), which discloses a pharmaceutical preparation containing ionic magnesium combined with additional therapeutic substances for the treatment and control of vasoconstriction and related conditions.

The Office Action states at page 3, lines 1-7 that:

> Richardson teaches an oral pharmaceutical composition comprising a dual layer combination tablet which is divided into two portions, one that is fully released into the stomach upon ingestion, and the other protected by an acid-resistant coating for release only in the intestine, whereby the intestine-release portion contains magnesium compounds/magnesium salts in combination with additional active agents and therapeutic substances, such as calcium and calcium salts (see reference column 6, line 62 through col. 11, line 55).

The dual layer combination tablet disclosed by Richardson combines calcium and magnesium so that they are simultaneously released into the body. Richardson does not disclose the sequential release of first calcium and then magnesium. The amended claims are directed to a composition having an immediate release portion that releases substantially all of the calcium component before the delayed release portion begins to release the magnesium component in the intestine. This minimizes the effect of calcium on the absorption of magnesium and thereby provides more efficient magnesium absorption. The use of a time release component to limit the interaction of calcium with magnesium is neither taught nor suggested by Richardson.

Richardson teaches "a combination tablet in which the components are divided into two portions, one that is fully released into the stomach upon ingestion, and the other protected by an acid-resistant coating for release only in the intestine" (col. 9, lines 35-38). In discussing the dual layer combination tablet, Richardson does not disclose that calcium is included in either the first or second layer of the dual layer tablet (col. 9, lines 34-53 and Example 2). Richardson only teaches that Vitamin E can be in the first layer and that it immediately releases upon ingestion. However, Richardson does not teach a preference for calcium in either the immediate release layer or in the delayed release layer.

The combination of magnesium and calcium taught by Richardson is substantially different from the composition claimed in the present invention. Richardson teaches a "preparation [that] contains ionic magnesium combined with additional therapeutic substances in an interactive and complementary manner." Col. 3, lines 9-12. Richardson also teaches that "[a]dditional active agents are optionally included in the formulations" and that "[e]xamples [of the additional active agents] are calcium and calcium salts." Col. 7, lines 62-63 and 65. Thus, Richardson only teaches that calcium can be "included in the formulations" as an active agent (col. 7, lines 62-66) in combination with magnesium. There is no teaching nor suggestion in Richardson of a dual component tablet where one component consists essentially of one or more magnesium compounds and the second component consists essentially of one or more calcium compounds.

Richardson does not teach a formulation or a two-layer tablet containing calcium and magnesium where the two components are <u>not</u> simultaneously released into the body. The

time release layer of Richardson's dual layer tablet does not prevent calcium from interacting with magnesium. Moreover, the Richardson `849 patent does not teach the benefits of separating the calcium component from the magnesium component as required by the amended claims of the present invention. One of ordinary skill in the art would not find it obvious from the teachings of Richardson to form a dual component tablet having calcium in the immediate release component and magnesium in the delayed release component.

The present invention specifically teaches that calcium should not be combined with magnesium because it interacts with magnesium and decreases the absorption of magnesium by the body.

> The present invention is an orally administered pharmaceutical composition which provides controlled release of magnesium and includes a magnesium component, a controlled-release component and an interactive agent component. The interactive agent component [i.e., calcium] includes an agent which interacts with the host to affect bio-uptake of magnesium by the host. **If the two components are released simultaneously in the gastrointestinal tract, the absorption of magnesium decreases.** Therefore, the interactive agent component is released in the stomach and the release of the magnesium component is released in the intestine. The interactive agent dissolves in the gastric juice of the stomach and substantially all of the interactive agent is released before passage into the intestine of the host. The magnesium component includes magnesium or a magnesium compound and a release-controlling agent which substantially prevents release of magnesium until passage out of the stomach and into the intestine of the host.
>
> Specification, p. 7, lines 2-12. (Emphasis added.)

Richardson merely teaches that a formulation can include a combination of magnesium and calcium, wherein both components are released into the host simultaneously. Richardson does not teach that the interaction of calcium with magnesium prevents the

efficient absorption of magnesium, nor does Richardson teach that formulations containing calcium and magnesium should include a means for limiting their interaction.

Applicants have amended the claims to more clearly define their invention. The applicants' composition includes a calcium component which consists essentially of one or more calcium compounds that immediately release in the stomach and a magnesium component which consists essentially of one or more magnesium compounds that release-in the intestine. The two components of the composition cannot include both a magnesium component and a calcium component. The amended claims, are therefore, clearly distinguishable from Richardson which teaches a two component composition wherein both components include magnesium. Accordingly, the amended claims of the present invention are not obvious in view of the Richardson `849 patent.

Claims 13, 14 and 18 have been rejected under 35 U.S.C. 103(a) as being unpatentable over the `849 patent as applied to claims 1-12 and 15-17, and further in view of U.S. Patent No. 5,811,126 to Krishnamurthy et al. ("Krishnamurthy" or "the `126 patent") or U.S. Patent No. 4,339,428 to Tencza ("Tencza" or "the `428 patent"). The Office Action states (at page 5, lines 14 to 20) that Richardson discloses a formulation with a delay release of both magnesium and calcium in the intestine.

> Richardson, as discussed above, teaches an oral pharmaceutical composition comprising a dual layer combination tablet which is divided into two portions, one that is fully released into the stomach upon ingestion, and the other protected by an acid-resistant coating for release only in the intestine, whereby the intestine-release portion contains magnesium compounds/magnesium salts

in combination with additional active agents and therapeutic substances, such as calcium and calcium salts.

Unlike Richardson, the composition of the present invention does not delay release both magnesium and calcium in the intestine. Instead, the amended claims of the present invention require a composition which immediately releases calcium in the stomach and delays the release of magnesium until it reaches the intestine. Richardson neither teaches nor suggests releasing the calcium component separately from the magnesium component in order to limit the interference of calcium with the absorption of magnesium.

The Office Action states at page 6, lines 3-4 that, "Krishnamurthy teaches a controlled release pharmaceutical composition for oral administration comprising a mixture of magnesium salt and calcium salt." Krishnamurthy teaches mixing calcium and magnesium together and does not teach nor suggest a means for preventing them from interacting when released in the body. As discussed in more detail above with regard to Richardson, the amended claims of the present invention specifically require the separation of magnesium and calcium into two different components so that the calcium can be released immediately and the magnesium can be delay released after substantially all of the calcium has been released. Such a sequential release of the two components would not be possible if they were mixed together as Krishnamurthy teaches. Accordingly, Krishnamurthy teaches away from the composition of the present invention. Therefore, Krishnamurthy, when combined with Richardson, does not render the amended claims of the present invention obvious. Neither reference discloses a composition which has a first component consisting essentially of one or more calcium compounds that is released in the stomach, and a second component

consisting essentially of one or more magnesium compounds and a release-controlling agent that releases magnesium in the intestine in a manner that avoids substantial interaction between the two components.

The Office Action states at page 7, lines 1-3 that "Tencza teaches an oral pharmaceutical formulation comprising a combination of magnesium carbonate and calcium carbonate together with a magnesium oxide component." Tencza discloses a combination of calcium and magnesium which is similar to Richardson and Krishnamurthy, but quite different from the present invention. Tencza's combination fails to teach the composition of the present invention which has separate and not combined calcium and magnesium components. There is no teaching in Tencza that would make it obvious to one of ordinary skill in the art to separate the two components and release them into the host sequentially.

The formulations taught by Tencza do not have a delay release mechanism which prevents a first component consisting essentially of calcium and a second component consisting essentially of magnesium and a release-controlling agent from releasing at the same time and interacting. Tencza neither recognizes nor addresses the problem of decreased absorption of magnesium into the body when calcium and magnesium are released at the same time. The present invention solves this problem by providing a two-component composition wherein calcium contained in the first component releases immediately and magnesium contained in the delay release component and does not release until it reaches the intestine. Tencza, when combined with Richardson, neither teaches nor suggests the sequential release of calcium in the stomach and magnesium in the intestine since both

Tencza and Richardson teach formulations in which calcium and magnesium are mixed together and simultaneously released.

The applicants have found that a composition containing both calcium and magnesium is absorbed by the body most efficiently when the two components are released sequentially. Sequential release of calcium in the stomach and magnesium in the intestine decreases the interaction between the two components and prevents the calcium from significantly interfering with the absorption of magnesium.

Richardson, Krishnamurthy and Tencza, either alone or in combination, fail to disclose the sequential release of a first component which is essentially calcium and a second component which is essentially magnesium and a release-controlling agent in order to avoid interaction between the two components. Moreover, there is no teaching nor suggestion in any of these references that would make the present invention obvious to one of ordinary skill in the art. Accordingly, the applicants respectfully request that the rejection of the claims as obvious in view of the cited art be withdrawn and that the amended claims be allowed.

Respectfully submitted,

Kevin E. McDermott
Registration No.: 35,946
Attorney for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
(516) 822-3550
184610_1